REMARKS

In view of the following remarks, the Examiner is respectfully requested to allow Claims 1 to 27, the only claims pending and currently under examination in this application.

The Examiner is thanked for the personal interview held with Dr. Galer and Mr. Field on May 23, 2006. During the interview, the distinction between peripherally induced and central nervous system induced headaches was reviewed. Furthermore, the '772 reference was reviewed and demonstrated to be concerned solely with headaches arising from peripherally induced mechanisms, and not headaches arising from central nervous system mechanisms, such as migraine headaches. Amendments were discussed which would obviate the rejections. Finally, the 112, 1st paragraph rejection was discussed and the Examiner indicated that, in view of the experimental results and description provided in the specification, this rejection would be withdrawn.

Amendment to the Inventorship

Applicants hereby request to add Lawrence Newman as an inventor, pursuant to 37 C.F.R. § 1.48(c). Amendments introduced above which include claims to previously unclaimed subject matter necessitate this amendment to the inventorship. Enclosed with this response please find Enclosure A which includes the requisite: (1) statement by Lawrence Newman; (2) new Oath or Declaration including all of the inventors' signatures; and (3) written consent by the assignee of the originally named inventors in the form of the enclosed statement pursuant to 3.73(b). Also enclosed with this response is the requisite processing fee pursuant to 37 C.F.R. § 1.17(i).

Amendment to the Specification

Applicants have amended the specification to make a claim to priority to the filing date of U.S. Patent Application serial no. 09/755,592, pursuant to 37 C.F.R. § 1.78(a)(3). The entire delay between the date the claim was due under paragraph 37 C.F.R. § 1.78(a)(2)(ii) and the present request was unintentional. Enclosed with this response as Enclosure B is a separate request. Also enclosed with this response is requisite processing fee pursuant to 37 C.F.R. § 1.17(t).

Amendment to the Claims

Claims 1, 6 and 11 have been amended to indicate that the headache pain to be ameliorated is pain caused by a tension headache, migraine headache or cluster headache. New Claim 27 has been added. Support for new Claim 27 may be found at page 8, lines 10 to 13. Accordingly, no new matter has been added.

As no new matter has been added by way of these amendments, entry thereof by the Examiner is respectfully requested.

Claim Rejections - 35 U.S.C. § 112, second paragraph

Claims 1 to 26 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking adequate written description.

According to the MPEP § 2163.02, to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. Possession may be shown in a variety of ways including description of an actual

reduction to practice or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention.

The Office asserts that the specification has not described the topical formulations for delivering NSAIDs because the specification has assertedly not set forth the dose of the drug to be delivered or other ingredients, such as carriers and enhancers, which may be used to carry the drug and facilitate its transport across the stratum cornium.

The Applicants respectfully disagree and contend that the Applicants have set forth an actual reduction to practice in view of which one of skill in the art would recognize that the Applicants had possession of the claimed invention.

As can be seen with reference to Example I, the Applicants have set forth an actual working example of the claimed invention. The claims as amended are directed to a method for ameliorating the pain caused by a tension headache, migraine headache or cluster headache. The method includes the step of topically applying a formulation that contains only an NSAID as the active agent to a keratinized skin surface of the head. The specification sets forth a specific example wherein an NSAID patch formulation is administered in accordance with the methods of the invention to woman with a history of migraine headaches and the headache pain was relieved. See page 9, lines 15 to 27.

Accordingly, in view of the Applicants actual reduction to practice one of skill in the art would recognize that the Applicants had possession of the claimed invention.

In addition, to further support the scope of the claims, the Applicants' specification additionally teaches that topical NSAID formulations and the methods of making them are well known in the art and cites and incorporates several patents

wherein suitable NSAID formulations for use in accordance with the Applicants' disclosed methods may be found. For instance, suitable formulations and their methods of production may be found in U.S. Pat. Nos. 4,670,254; 4,710,497; 4,740,374; 4,777,046; 4,956,171; 4,999,379; 5,204,119; 5,373,022; 5,374,661; 5,429,590; 5,695,779; 5,814,599. See page 4, lines 21 to 24.

Furthermore, the specification teaches that the NSAIDs can be formulated as a gel, a lotion, a cream, a patch, a hydrogel, aerosol or the like. See page 4, lines 14 to 24. Additionally, the specification teaches that suitable dose regimens are well known in the art and set forth in references such as the Physician's Desk Reference and the Merck Index. For instance, the specification teaches that although the amount may vary, the typical amount of NSAID present in a topical formulation generally ranges from about 0.1 to about 5.0% w/w, usually from about 0.5 to about 3.0% w/w and more usually from about 0.5 to about 2.0% w/w. See page 5, lines 17 to 23. Further still, the specification teaches how and where to apply the NSAID formulation, teaches the use of patch formulations, and teaches the time period during which the formulation is to be applied. See page 6, line 7 to page 7, line 18.

Accordingly, contrary to the assertion of the Office, the Applicants' have set forth a description of an actual reduction to practice of the claimed invention, have taught specific formulations of NSAIDs and have also cited several references wherein the manner of producing such formulations and the constituents thereof may be found. Furthermore, the Applicants' specification teaches how to deliver the disclosed NSAID formulations, sets forth representative amounts to be delivered and gives examples of suitable time periods for the administration of exemplary NSAID formulations.

Hence, in view of the Applicants' reduction to practice and the extensive teachings of both NSAID formulations and their methods of use, and especially

when coupled with the skilled artisan's common knowledge of how to generally produce NSAID formulations, the Applicants contend that one of skill in the art in view of the Applicants' disclosure would not doubt that the Applicants had possession of the claimed subject matter.

Therefore, in view of the above the Applicants respectfully request that the § 112, first paragraph, written description rejection be withdrawn.

Claim Rejections - 35 U.S.C. § 102

Claims 1, 2, 5-7, 10, 11 and 24-26 have been rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Van Engelen *et al.* (U.S. Patent No. 6,416,772).

According to the MPEP, a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. Additionally, the identical invention must be shown in as complete detail as is contained in the claim. See MPEP 2131.

An element of the rejected claims as amended is the step of topically applying an effective amount of a topical NSAID formulation to ameliorate a headache pain caused by a tension headache, migraine headache or cluster headache.

Van Engelen, on the other hand, does not teach a method that includes the application of an NSAID formulation for the amelioration of headache pain caused by a tension headache, migraine headache or cluster headache. On page 6 of the Office Action mailed on March 30, 2006 the Office acknowledges that Van Engelen does not explicitly teach the claimed types of headaches.

Hence, in supporting this rejection, the Office assumes that all headaches are the same and that the formulation disclosed in Van Engelen would be expected to be effective for treating any kind of headache, such as a tension headache, cluster headache or migraine headache.

The Applicants, however, disagree, and contend that not all headaches are the same. As reviewed during the personal interview with the Examiner, headaches may be caused by a mechanism that is localized to peripheral tissue or they may be caused by an underlying disturbance in the central nervous system, most commonly within the brain. Accordingly, the underlying pathophysiology and symptomology of headache pain caused by a localized peripheral mechanism is dramatically different from headache pain caused by a disturbance in the central nervous system.

Migraine, cluster and tension headache pains are all believed to be caused by different disturbances in the central nervous system. Accordingly, migraine, cluster and tension headache conditions are considered unique clinical entities distinct from those of headache pains caused by localized peripheral mechanisms (e.g., muscle contractions). See the enclosed Declaration of Dr. Bradley Galer provided in Enclosure C to this response.

The symptoms to be treated by the compositions set forth in Van Engelen include muscular aches, strains and cramps, arthritis, joint pain, burns, lower back discomfort, bursitis, rheumatism, insect bites, and sports injuries, athlete's foot, shingles, headaches, menstrual cramps, and tennis elbow. See column 3, lines 56 to 62. All of these listed conditions are caused by a known peripheral mechanism, namely, inflammation and muscle contractions in the peripheral tissues, joints, muscles or peripheral nerves. Additionally, with respect to Example 2, the headache condition to be treated appears to have resulted from a peripheral mechanism because there is no mention of the associated nausea,

vomiting and/or light/sound sensitivities, or eye symptoms that are commonly associated with headache conditions that are caused by an underlying disturbance in the central nervous system.

Therefore, one of skill in the art in diagnosing and treating headache conditions would conclude that the "headache" condition to be treated in Van Engelen is one that has a peripheral mechanism of origin. That is a headache of this nature is believed to be caused by peripheral mechanisms such as muscle contractions.

Accordingly, Van Engelen can only be considered as treating a headache that is caused by a peripheral mechanism. Because Van Engelen can only be considered as disclosing the treatment of a headache that is caused by peripheral mechanisms, Van Engelen does not teach treating a headache pain caused by a disturbance in the central nervous system, such as Migraine Headache, Cluster Headache, Indomethacin Responsive Headaches, and Chronic Tension Type Headache. Hence, Van Engelen does not teach ameliorating a headache pain caused by a tension headache, migraine headache or cluster headache.

In view of the above, the assumption by the Office is erroneous as not all headache pains are the same and not all headache pains can be treated in the same manner. Because Van Engelen does not teach a method that includes the application of an NSAID formulation for the amelioration of headache pain caused by a Migraine Headache, Cluster Headache, Indomethacin Responsive Headaches, and Chronic Tension Type Headache, Van Engelen does not teach every element of the rejected claims. Therefore, the Applicants contend that Van Engelen is deficient and does not anticipate the claimed invention. Accordingly, the Applicants respectfully request that the 35 U.S.C. § 102(e) rejection of Claims 1, 2, 5-7, 10, 11 and 24-26 be withdrawn.

Claims 1-13, 16 and 19-26 have been rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Galer *et al.* (U.S. Publication No. 2002/0143047).

The Office asserts that the Galer application is available as 102 (e) prior art with respect to the instant application.

However, according to the M.P.E.P. § 2136.05, a 35 U.S.C. § 102 (e) rejection may be overcome by showing that the cited prior art reference is describing the Applicants' own work.

In the present case, the inventorship of the present application now includes all of the inventors of the 2002/0143047 application. In addition, the priority of the present application has been amended to claim priority to the 2002/0143047 application. Finally, enclosed is a 37 C.F.R. § 1.132 declaration (Provided as Enclosure D) which states that, to the extent the 2002/0143047 application describes the claimed invention of the present application, it is describing the applicants own work.

Therefore, in light of the 1.132 declaration by Galer, Caldwell and Newman, the 2002/0143047 application is not available as 102 (e) prior art to the present application. Accordingly, because the 2002/0143047 application is not available as prior art to the instant application the Applicants respectfully request that the 35 U.S.C. § 102(e) rejection of Claims 1-13, 16 and 19-26 be withdrawn.

Claim Rejections - 35 U.S.C. § 103

Claims 1, 2, 5-7, 10, 11, 14-18 and 24-26 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Van Engelen *et al.* (U.S.

Patent No. 6,416,772) in view of Toppo (U.S. Patent No. 5,318,960).

According to the MPEP § 706.02 (j), to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teags. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

An element of the rejected claims as amended is the step of topically applying an effective amount of a topical NSAID formulation to ameliorate a headache pain caused by Migraine Headache, Cluster Headache, Indomethacin Responsive Headaches, and Chronic Tension Type Headache.

As set forth above and reviewed in the enclosed 1.132 declaration of Dr. Bradley Galer, Van Engelen is deficient in that it does not teach a method that includes the application of an NSAID formulation for the amelioration of headache pain caused by a Migraine Headache, Cluster Headache, Indomethacin Responsive Headaches, and Chronic Tension Type Headache. Van Engelen does not suggest this method because Van Engelen only discloses the administration of a composition for the treatment of a headache that is caused by a peripheral mechanism. As described above, Migraine Headache, Cluster Headache, Indomethacin Responsive Headaches, and Chronic Tension Type Headache are <u>not</u> caused by a peripheral mechanism. As Toppo was cited solely for its disclosure of the specific NSAIDs: indomethacin, ketoprofen, diclofenac and ibuprofen it fails to remedy the deficiencies of Van Engelen. Therefore, a *prima facie* case of obviousness has not been established because the recited combination fails to teach every element of the rejected claims.

Additionally, even if the recited combination were to teach all the elements of the rejected claims and a *prima facie* case of obviousness were to be established, the Applicants rebut the *prima facie* case of obviousness because of the unexpected results of the Applicants' claimed invention.

As stated above, the pathophysiological mechanism behind Migraine Headache, Cluster Headache, Indomethacin Responsive Headaches, and Chronic Tension Type Headache is believed to be in and/or caused by a disturbance in the central nervous system. Because the mechanism behind these headache pains is not in a peripheral tissue, but rather in the central nervous system, one of skill in the art would not have expected a topically applied composition that results in very small amounts of active medication, believed to be subtherapeutic, to reach the bloodstream to be effective for ameliorating pains caused by Migraine Headache, Cluster Headache, Indomethacin Responsive Headaches, and Chronic Tension Type Headache. One would not have expected this result because the source of pain for these headaches is thought to be located in the brain, which is protected by the skin, bones of the skull, blood brain barrier, and the like. It was indeed surprising to the inventors that the pain and other symptoms of Migraine and Indomethacin Responsive Headaches was significantly alleviated by topical application of an NSAID. See the enclosed declaration of Dr. Bradley Galer (Enclosure C).

Therefore, prior to the Applicants' work in the field it was unexpected that a topically applied NSAID formulation could pass through all of these barriers and be able to effect a change in the central nervous system so as to ameliorate a headache pain associated with a Migraine Headache, Cluster Headache, Indomethacin Responsive Headaches, and Chronic Tension Type Headache. In fact, conventional treatments for these types of headaches at the time of filing of

the Applicants' application involved the systemic administration of medicaments into the recipient's blood stream. As can be seen from Example I, although unexpected, the Applicants were the first to show that the pain associated with a Migraine Headache, Cluster Headache, Indomethacin Responsive Headaches, and Chronic Tension Type Headache could be ameliorated with the topical application of an NSAID formulation.

In view of the above, the Applicants contend that a *prima facie* case of obviousness has not been established because the combination of Van Engelen and Toppo fails to teach or suggest every element recited in the rejected claims. Alternatively, even if the recited combination were to teach all the elements of the rejected claims and a *prima facie* case of obviousness were to be established, the Applicants rebut the *prima facie* case of obviousness because of the unexpected results of the Applicants' claimed invention. Accordingly, the Applicants contend that the combination fails to render Claims 1, 2, 5-7, 10, 11, 14-18 and 24-26 obvious and, therefore, respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 1, 2, 5-7, 10, 11, 14-18 and 24-26 be withdrawn.

Claims 1 to 26 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Van Engelen *et al.* (U.S. Patent No. 6,416,772) in view of Oda (U.S. Patent No. 5,725,874).

An element of the rejected claims as amended is the step of topically applying an effective amount of a topical NSAID formulation to ameliorate a headache pain caused by Migraine Headache, Cluster Headache, Indomethacin Responsive Headaches, and Chronic Tension Type Headache.

As set forth above, Van Engelen is deficient in that it does not teach a

method that includes the application of an NSAID formulation for the amelioration of headache pain caused by a Migraine Headache, Cluster Headache, Indomethacin Responsive Headaches, and Chronic Tension Type Headache. Van Engelen does not suggest this method because Van Engelen only discloses the administration of a composition for the treatment of a headache that is caused by a peripheral mechanism. As described above, Migraine Headache, Cluster Headache, Indomethacin Responsive Headaches, and Chronic Tension Type Headache are not caused by a peripheral mechanism. As Oda was cited solely for its disclosure of a percutaneous absorbable patch and cream formulation which includes the specific NSAIDs: indomethacin, ketoprofen, diclofenac and/or ibuprofen it fails to remedy the deficiencies of Van Engelen. Therefore, a *prima facie* case of obviousness has not been established because the recited combination fails to teach every element of the rejected claims.

Additionally, even if the recited combination were to teach all the elements of the rejected claims and a *prima facie* case of obviousness were to be established, the Applicants rebut the *prima facie* case of obviousness because of the unexpected results of the Applicants' claimed invention.

As stated above, prior to the Applicants work in the field it was unexpected that a topically applied NSAID formulation could pass through all of these barriers and be able to effect a change in the central nervous system so as to ameliorate a headache pain associated with a Migraine Headache, Cluster Headache, Indomethacin Responsive Headaches, and Chronic Tension Type Headache. In fact, conventional treatments for these types of headaches at the time of filing of the Applicants' application involved the systemic administration of medicaments into the recipient's blood stream. Hence, the Applicants were the first to show that the pain associated with a Migraine Headache, Cluster Headache, Indomethacin Responsive Headaches, and Chronic Tension Type Headache

could be ameliorated with the topical application of an NSAID formulation.

In view of the above, the Applicants contend that a *prima facie* case of obviousness has not been established because the combination of Van Engelen and Oda fails to teach or suggest every element recited in the rejected claims. Alternatively, even if the recited combination were to teach all the elements of the rejected claims and a *prima facie* case of obviousness were to be established, the Applicants rebut the *prima facie* case of obviousness because of the unexpected results of the Applicants' claimed invention. Accordingly, the Applicants contend that the combination fails to render Claims 1 to 26 obvious and, therefore, respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 1 to 26 be withdrawn.

Claims 14, 15, 17 and 18 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Galer *et al.* (U.S. Publication No. 2002/0143047) in view of Toppo (U.S. Patent No. 5,318,960).

The 2002/0143047 publication was filed on January 5, 2001 and published on October 3, 2002. The instant application was filed December 26, 2001. Accordingly, the 2002/0143047 publication was filed before but published after the filing of the present application. Hence, the 2002/0143047 publication can only be considered for the purposes of 35 U.S.C. § 103 (a) as constituting prior art to the instant application under 35 U.S.C. § 102 (e).

As stated above, in light of the amendment to inventorship and claim to priority, as well as the enclosed 1.132 declaration filed herewith, the 2002/0143047application is not available as 102 (e) prior art to the present application. Accordingly, because the Galer application is not available as prior

art to the instant application it cannot be used to render the presently claimed invention obvious. The Applicants, therefore, respectfully request that the 35 U.S.C. § 103 (a) rejection of Claims 14, 15, 17 and 18 be withdrawn.

CONCLUSION

The Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, reference no. CALD-007.

Respectfully submitted,

Date: June 26, 2006

By: _____
Bret E. Field
Registration No. 37,620

Encs:
Enclosure A) Amendment to Inventorship Documents:
(1) statement by Lawrence Newman;
(2) new Oath or Declaration including all of the inventors' signatures;
(3) written consent by the assignee of the originally named inventors in the form of the enclosed statement pursuant to 3.73(b).
Enclosure B) Petition to amend claim to priority
Enclosure C) 1.132 declaration of Dr. Bradley Galer.
Enclosure D) 1.132 declaration by Galer, Caldwell and Newman
Change of inventorship processing fee pursuant to 37 C.F.R. § 1.17(i)
Amendment to claim to priority processing fee pursuant to 37 C.F.R. § 1.17(t)

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue, Suite 200
East Palo Alto, California 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231